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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 38

Application Number: 08/126,505
Filing Date: September 24, 1993
Appellant(s): Atkinson et al.

Patrea L. Pabst
For Appellant

EXAMINER'S ANSWER

This is in response to appellant's brief on appeal filed January 4, 1999.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement to the effect that there are no related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is incorrect.

The amendment after final rejection filed on 9/15/98 has been entered due to the grant of the petition filed 11/24/98. The petition was decided September 8, 2000; see paper number 37.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is substantially correct. The changes are as follows: Due to the grant of the petition filed 11/24/98, the rejection of claims 10 and 25 under 35 U.S.C. §112, second paragraph, has been overcome, and the rejection is accordingly withdrawn. Hence, the only claims currently rejected under 35 U.S.C. §112, second paragraph, are claims 8, 9, 23 and 24.

(7) Grouping of Claims

The appellant's statement in the brief that certain claims do not stand or fall together is not agreed with because appellants state at page 3 of the appeal brief that the claims require a different analysis of the art. However, no such 'different analysis' is presented for the proposed groups of claims. The Examiner suggests that the claims should fall into two mutually exclusive groups: Group I consists of claims 8-9, 23 and 24, which are rejected under 35 U.S.C. §112, second paragraph, and Group II consists of claims 1, 3, 12, 13, 15, 16, 18, 27, 28 and 30-32, all rejected under 35 U.S.C.

§103(a) as being obvious over a single group of prior art references. As all of the claims of Group II are rejected over the same art, which collectively addresses all of the limitations of each of the claims, the Examiner does not find basis for further division into additional groups of claims.

(8) Claims Appealed

It is noted that appellants prudently included two appendices of claims to the brief, Appendix I presuming non-entry of the after final amendment of 9/15/98, and Appendix II presuming entry of that same amendment.

The copy of the appealed claims contained in Appendix II to the brief is correct.

(9) Prior Art of Record

The following is a listing of the prior art of record relied upon in the rejection of claims under appeal.

C.A. Lowell et al., "Mapping of the Epstein-Barr virus and C3dg binding sites to a common domain on complement receptor type 2", J. Experimental Medicine, volume 170, pages 1931-1946. December 1989.

J. P. Atkinson et al., "Separation of self from non-self in the complement system", (Immunology Today, 1987, volume 8, pages 212-215; Ref. 1-AT.

WO 89/01041, I. W. Caras et al., 2/9/89.

5,256,642	Fearon et al.	10/26/93
4,935,233	Bell et al.	6/19/90

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 8-9 and 23-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 8-9 and 23-24 are indefinite with respect to the recitation in these claims of the recitation "or these amino acid sequences where I is replaced with either L or V, L is replaced with either I or V, V is replaced with I, L, or F, F is replaced with V, K is replaced with R, R is replaced with K, SEQ ID NO: is replaced with N, N is replaced with Q, D is replaced with E, E is replaced with D, G is replaced with A, or A is replaced with G." As stated in the advisory action mailed 10/20/98, paper number 33, is it not clear whether all instances of a given residue are to be substituted, i.e. wither all "I" residues are to be replaced by either L or V, or only some of the I residues, or only a single I residue, and if so, which one.

It is noted that in the final Office Action, paper number 28, this grounds of rejection was stated as being due to the indefiniteness of the recitation "structurally similar amino acids . . . (I, L,V), (F/V) . . . and combinations thereof" because the claims did not make clear how "structurally similar amino acids" are related to the recited groups of amino acids, and because it was unclear whether "combinations thereof" refers to combinations of the structurally similar amino acids or to combinations of the various amino acid substitutions recited in the claim. The petition which resulted in entry of the amendment states that "it is concluded that the amended claims are of the same or similar scope as the claims prior to amendment and therefor (sic) the amendment should have been entered as it clarifies the limitations of the claims and may reduce the issues on appeal." While the

amendment may clarify and reduce the issues on appeal, in that the completely indefinite language "structurally similar amino acids . . . (I, L,V), (F/V) . . . and combinations thereof" has been replaced by the less, but still indefinite "I is replaced with either L or V, L...", the language as a whole remains indefinite under 35 U.S.C. §112, second paragraph, for reasons stated above, and therefore this rejection is maintained.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3, 12-13, 15-16, 18, 27-28 and 30-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lowell et al. in view of Fearon et al. (U.S. Pat. No. 5,256,642), Caras (WO 89/01041), Atkinson et al. (Immunology Today, 1987, 8, 212-215; Ref. 1-AT) and Bell et al. (U.S. Pat. No. 4,935,233).

Lowell teaches chimeric CR1/CR2 protein analogs including one in which the first two SCRs of CR2 are substituted for the first two SCRs of CR1 (CR2/CR1 XE) (see Fig. 1, p. 1936 and p. 1939). Lowell teaches a method to express the analog recombinantly which includes construction of DNA encoding the protein analog, transfection into host cells, and expression of the analog (pp. 1933-1935). Lowell also discloses that cells expressing the chimeric protein were incubated with PBSA, which constitutes a pharmaceutical carrier (p. 1935). Although Lowell does not disclose that

the chimeric protein CR2/CR1 XE binds either C3b or C4b, as recited in the claims, it was known in the prior art as evidenced by applicants admissions at page 5 of the specification that the first two SCRs of CR1 are required for C4b binding while SCRs 8-9 (and possibly SCR 10) and SCRs 15-16 (and possibly SCR 17) constitute two C3b binding sites (see p. 5 of specification and Klickstein, 1988). Thus, CR2/CR1 XE would inherently bind C3b (via the CR1 SCRs) and would also inherently bind C3dg and EBV (via the CR2 SCRs). Therefore, although Lowell does not disclose it explicitly, Lowell teaches a chimeric RCA protein analog which binds not only the ligand of the native protein from which it was derived, in this case C3b, but which also binds a ligand to which the native protein cannot bind, in this case C3dg and EBV. Lowell also teaches that is was well known in the art at the time the invention was made that the RCA proteins are composed of SCR domains which are highly similar to one another (pp. 1931-1932). Lowell also teaches that each SCR is likely to interact only with adjacent SCRs, such that removal of SCRs not involved in ligand binding should not alter ligand binding, and further discloses that chimeric protein analogs (fusion proteins) comprising SCR domains from these genetically related proteins would be likely to result in functional chimeric proteins (pp.1942-1943). Lowell does not teach or suggest making a chimeric RCA protein analog other than CR1/CR2, as recited in the instant claims.

Caras teaches that a soluble DAF can be used to inhibit complement activation *in vivo*, for the treatment of autoimmune and inflammatory diseases (p. 5), and Fearon teaches that a soluble CR1 can be used to inhibit inappropriate complement activation *in vivo*, for the treatment of such disorders as inflammatory and autoimmune diseases (col. 25, lines 18-43). Both Fearon and Caras also teach that ligand-binding fragments of CR1 and DAF, respectively, can be used therapeutically (col. 24, lines 17-37 and p. 7). Furthermore, Atkinson teaches that all of CR1, DAF, MCP, C4bp and Factor H are critically important in regulation of complement activation (pp. 213-214). Thus, since Fearon and Caras teach that CR1 and DAF can be administered *in vivo* to inhibit autoimmune and inflammatory diseases and Atkinson teaches that CR1 and DAF, as well as the other RCA proteins, have interrelated effects in controlling the complement system, one having ordinary skill in the art

would expect that administration of CR1 and DAF together would have additive effects in inhibiting inflammatory and autoimmune diseases.

Bell teaches chimeric proteins formed from covalently linked polypeptide cell modulators wherein the two modulators have different but complementary activity (col. 2, lines 3-29). Bell also discloses that a chimeric protein can be used to produce an enhanced effect than a single dosage form (col. 2, lines 32-36).

It would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the chimeric CR1/CR2 protein taught by Lowell and substitute for the CR2 SCRs the SCRs of DAF, in order to produce a chimeric protein which would have C3b binding (via CR1) and DAF activity. Furthermore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the chimeric protein taught by Lowell and make an RCA analog in which the ligand-binding SCRs of DAF are linked to the entire soluble CR1, rather than have substitution of the two N-terminal SCRs of CR2 for the two N-terminal SCRs of CR1, in order to obtain a chimeric RCA molecule which could bind C3b and C4b and have decay accelerating activity. One would be motivated to make these modifications in order to obtain a molecule which could be used therapeutically to additively inhibit complement activation through binding of C3b and/or C4b, and through its decay accelerating activities as taught by Bell. One would be motivated to make either the full-length CR1/DAF chimeric protein or a CR1/DAF chimeric protein in which the first two SCRs of CR1 are missing because one would expect that administration of CR1 and DAF would have additive effects in inhibiting complement activation, and Bell teaches that administration of a chimeric protein will have the effect of the two single effectors administered separately. It also would have been obvious to one having ordinary skill in the art to make this chimeric protein using DNA encoding such a protein, expression vectors and host cells to recombinantly produce this protein, because Lowell used this method to make CR1/CR2 and because Bell teaches that chimeric proteins are preferably made by genetic engineering (col. 2, lines 37-44). Furthermore, one would have had a reasonable expectation of success because Lowell teaches that

chimeric proteins containing the structurally and functionally similar SCR domains of CR2 were able to bind their native ligands in the CR2/CR1 chimera.

(11) Response to Argument

At page 9 of the appeal brief, appellants argue that since Lowell never looks at or predicts that one can alter functional activity in a chimeric protein, but rather discusses only the binding activity of the chimeric protein. This argument is unpersuasive because the rejection that is instantly made is based not only upon Lowell but upon other references which would render the claimed invention obvious. The teachings of Lowell, as set forth above, *in combination* with the other references cited in the rejection, render the claimed invention as a whole obvious over the cited prior art for reasons set forth above.

In the paragraph bridging pages 9-10 of the appeal brief, appellants argue that they were the first to determine which SCRs were responsible for particular different activities and homologous in terms of structure and functions, and that "Only appellant made truncated complement regulatory proteins and determined that as few as three SCRs were required for activity." This argument has been fully considered but is not deemed persuasive because while appellants dissection of structure and function may be scientifically interesting, it remains that the cited prior art provides ample teachings of why and how to make the claimed proteins. Further, while appellants may indeed have been the first to determine that as few as three SCRs were required for activity, there is no corresponding limitation in the claims, which use open language (to use claim 1 as an example) in which *one* of the members of the Markush group may be "complement regulating protein analogs consisting of *as few as* three short consensus repeats". An open, lower limit does not exclude the species rendered obvious by the cited prior art.

The Examiner disagrees with appellants assertion at the top of page 10 that it was not known at the time the invention was made that chimeric proteins comprising SCRs of different functions could be made. As stated above in the rejection, "although Lowell does not disclose it explicitly, Lowell teaches a chimeric RCA protein analog which binds not only the ligand of the native protein

from which it was derived, in this case C3b, but which also binds a ligand to which the native protein cannot bind, in this case C3dg and EBV." Therefore, such had been actually accomplished prior to appellants invention. Further, the teachings of Bell et al., as cited above, demonstrate that the person of ordinary skill in the art at the time the invention was made would have been motivated to make chimeric proteins combining multiple functions, and would reasonable have expected each portion of the chimer to retain its respective function.

Applicants argument of Caras, Fearon and Bell continue to argue the respective references singly, rather than in the combination in which they are cited. Appellants argument attempts to address the references in isolation, rather than as a collective example of what would have been obvious to the person of ordinary skill in the art at the time the invention was made. One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In the heading toward the end of page 10 of the appeal brief, appellants declare that a *prima facie* case of obviousness cannot be established by hindsight reconstruction. It must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In this case, appellants allege at page 11 that "One could not have predicted that changing domains within a protein could confer a discrete activity since these are extremely large and complex proteins, and one would predict steric hindrance and other factors to interfer (sic) with the transfer of activity." This argument has been fully considered but is not deemed persuasive because, as stated in the rejection, Lowell teaches that each SCR is likely to interact only with adjacent SCRs, such that removal of SCRs not involved in ligand binding should not alter ligand binding, and further discloses that chimeric protein analogs comprising SCR domains from these genetically related proteins would be likely to result in functional chimeric proteins (pp.1942-1943).

Thus, the primary reference provides teachings contrary to appellants assertion. Appellants assertion that the result is unexpected is not supported by any art of record, nor have appellants provided any support for the assertions. Appellants argument that the invention is not obvious because only appellants ever actually tested constructs for binding has been fully considered but is not deemed persuasive because in essence, this is an argument that the results are unexpected, which as stated in this paragraph is not supported by the prior art or any information of record, and indeed is not consistent with the prior art cited in the rejection, and further, because this rejection is under 35 U.S.C. §103(a), on the basis of obviousness, and not under 35 U.S.C. §102 on the basis of anticipation. It is not necessary that the invention previously have been made, as required under 35 U.S.C. §102, merely that it have been obvious to the person of ordinary skill in the art at the time the invention was made. The Examiner maintains that it is, for reasons stated above.

Regarding the rejection under 35 U.S.C. §112, second paragraph, appellants merely state that "It is believed that the terminology used in the claim is in very common usage among those skilled in the art and would be clearly and unambiguously understood." This argument has been fully considered but is not deemed persuasive for several reasons: First, although appellants allege the language to be unambiguous, they have not disclosed what they feel the correct interpretation to be. It is noted that the Examiner's precise reasons for finding the language indefinite were of record in the advisory action mailed 10/20/98, whereas appellant's brief was filed January 4, 1999. Accordingly, although appellants were on notice that the current language was still considered to be indefinite, they have chosen not to disclose what it is they feel the supposed 'unambiguous' meaning of the language to be. Second, appellants have not pointed out any examples in the art of the term usage that they urge to 'very common'. Further, it is often the case that terms are 'common' in the scientific community without having the type of clear and unambiguous meaning that is required by 35 U.S.C. §112, second paragraph. Accordingly, appellants arguments are not persuasive.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Lorraine Spector
Primary Examiner
Art Unit 1647

Gary Kunz
Supervisory Primary Examiner
Art Unit 1647
(Conferee)

Christopher S. Low
Supervisory Primary Examiner
Art Unit 1653
(Conferee)

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ARNALL GOLDEN & GREGORY LLP
2800 One Atlantic Center
1201 West Peachtree Street
Atlanta, Georgia 30309-3450